

## **REMARKS**

Following entry of the instant amendment, Claims 4, 5, 15, 17, 18, 20-27, 30-40, 42, and 43 are pending and under consideration. The claims as currently pending are attached hereto as *Appendix D*.

### **I. Withdrawn Rejections**

Applicants note with appreciation that the rejection of Claims 4, 5 and 15, 17, 18, 20-27, 30-40, 42, and 43 under 35 U.S.C. §101 for double patenting is withdrawn.

Applicants further note with appreciation that the rejection under 35 U.S.C. 112, second paragraph, of Claims 4, 5, 25, 26, 39, and 40, as being indefinite, is withdrawn.

### **II. The Amendments**

#### **A. The Specification**

The Substitute Specification provided herewith as *Appendix B* is submitted to replace the Specification filed August 16, 2000. A marked-up version of the Substitute Specification is presented as *Appendix A*. No new matter is introduced with this Substitute Specification.

Replacement of the Specification of record with the Substitute Specification filed herewith under C.F.R. § 1.125 is respectfully requested. The Substitute Specification has been prepared to comply with the format required by the rules of practice. Additionally, the Substitute Specification has been amended to correct typographical errors. The changes do not introduce new matter. Accordingly, Applicants request entry of the Substitute Specification and the marked-up copy of the Substitute Specification into the instant application.

## **B. The Claims**

The claims have been amended, without prejudice, for the purpose of more clearly defining what Applicants regard as their invention. Specifically, Claims 21 and 37 have been amended. The amendment does not introduce new matter and merely corrects typographical errors. Entry of the claims under 37 C.F.R. § 1.111 is respectfully requested.

## **III. The Rejections**

### **A. Rejection of Claims 4-5, 15, 17-18, 23, 26-27, 32, 38, and 42-43 Under 35 U.S.C. §103(a)**

Claims 4-5, 15, 17-18, 23, 26-27, 32, 38, and 42-43 stand rejected under 35 U.S.C. §103(a) as being obvious over Srinivasan *et al.*, U.S. Patent No. 5,066,789 (“Srinivasan”), in view of Spector *et al.*, U.S. Patent No. 3,976,763 (“Spector”) and Wong, 1991, *Chemistry of Protein Conjugation and Cross-Linking*, CRC Press, pp. 63-67 (“Wong”). The rejection is respectfully traversed.

***The Legal Standard.*** In order to establish a *prima facie* case of obviousness, the Office must, *inter alia*, cite a combination of references that, taken as a whole, suggest the claimed invention. Applicants respectfully submit that the presently cited art does not suggest the claimed invention; therefore the Office has not established a *prima facie* case of obviousness.

***The Presently Claimed Invention.*** The presently claimed invention is directed to a conjugate useful for treating a tumoral, infectious, or autoimmune disease in a subject. The claimed conjugate comprises (a) an active substance useful for treating said disease selected from the group consisting of a chemotherapeutic agent and a photoactive compound, (b) a native human serum albumin that is not regarded as exogenous by the subject, and (c) a linker linking the active substance to the albumin, wherein the linker can be cleaved intracellularly, and wherein the linker

comprises an azo group. *See*, Claim 15. The invention is further directed to a process of preparing such conjugate, and to a method of treatment using such conjugate.

***The Cited References Do Not Suggest the Claimed Invention.*** Applicants respectfully submit that the combination of the cited references, *i.e.*, Srinivasan, Spector and Wong do not teach or suggest the presently claimed invention. In particular, the cited references, *inter alia*, do not teach or suggest a conjugate comprising an active substance and a native human serum albumin that is not regarded as exogenous by the subject, linked together by an azo bond that can be cleaved intracellularly. The mere fact that various *components* of the claimed conjugate, *i.e.*, a human serum albumin, an azo-bond containing linker, and various active substances, may be known in the art does not render the conjugate as a whole obvious.

Srinivasan relates to conjugates comprising a targeting substance and a diagnostic/therapeutic agent joined by a stabilized Schiff base or hydrazone linkage. Applicants argued previously that the conjugates taught by Srinivasan are unrelated to the conjugates of the present invention, as the conjugates disclosed in Srinivasan comprise a Schiff base linkage, rather than an azo group linkage, as presently claimed. As the skilled artisan will recognize, a Schiff base linkage is chemically different from an azo group, *i.e.*, a Schiff base entails an “-N=C-” bond, whereas an azo group is a “-N=N-” bond. Thus, a Schiff base linkage comprises a double bond between a nitrogen and a carbon, while an azo group comprises a double bond between two nitrogens. Due to the difference in free electrons, a Schiff base allows for *three* substituents, one at the N and one at the C, while the azo group allows only for *two* substituents. As a consequence of the unlike chemical makeup and functionality, a

Schiff base and an Azo bond have different physical chemical characteristics.

Therefore it cannot be obvious to substitute one by the other.

In response to Applicants' argument that a Schiff base is different from an azo bond as, *inter alia*, a Schiff base allows for three substituents, while an azo bond only allows for two, the Examiner states that as disclosed in Srinivasan, "two items are linked to the linker," referring to the conjugate depicted in Col. 3.

Applicants respectfully point out that the conjugate referred to by the Examiner comprises, consistent with Applicants' arguments, a Schiff base comprising a double bond between a nitrogen and a carbon, linking a target substance to a diagnostic or therapeutic agent. Further consistent with Applicants arguments, the Schiff base has three substituents, *i.e.*, the target substance, the diagnostic or therapeutic agent, and an "R" group. The conjugate disclosed in Srinivasan and referred to by the Examiner comprises a linker that clearly is chemically distinct from a linker comprising an azo bond. The two are not simply interchangeable due to their different chemical nature (*e.g.*, the azo bond would not allow for the additional "R" group. Therefore, it cannot be obvious to exchange the Schiff base disclosed in Srinivasan by an azo bond.

Further, in response to Applicants' argument that a stabilized Schiff base is not intracellularly cleavable, while an azo bond is, the Examiner refers to Col. 13 of Srinivasan to show that the disclosed conjugates may be intracellularly cleaved. In response to the Examiner's statements, the Applicants respectfully submit that while Srinivasan discloses that intracellular release of a cytotoxic agent may be desirable and that there may be an effect of aryl-groups substituted with electron-donating and/or electron-withdrawing groups on the rate of hydrolysis of the diagnostic or therapeutic agent from the targeting substance, the conjugates disclosed in Srinivasan

are still totally different from the presently claimed conjugates comprising an azo bond.

Neither of the cited secondary references cure the shortcoming of Srinivasan. While Spector discloses the use of a diazophenylcarbonyl linking group, it does not teach using an azo linkage to link a chemotherapeutic agent or a photoactive substance to a human serum albumin. As pointed out, *supra*, given the differences in the chemical nature of a Schiff base, as employed by Srinivasan, and an azo group, the Schiff base of the Srinivasan conjugates could not simply be substituted by the diazophenylcarbonyl linking group disclosed in Spector. Therefore, a combination of Srinivasan and Spector does not teach or suggest the claimed conjugates.

With regard to Wong, Applicants respectfully submit that also the teaching of Wong does not cure the deficiencies of Srinivasan and Spector. While Wong may show the “-N=N-” structure of an azo bond, it does not teach the use of an azo linkage to link a chemotherapeutic agent or a photoactive substance to a human serum albumin. Again, given the differences between the chemical nature of a Schiff base and an azo group, the Schiff base of the Srinivasan conjugates could not simply be substituted by the azo bond shown in Wong. Therefore, a combination of Srinivasan, Spector and Wong does not teach or suggest the claimed conjugates.

***There Is No Suggestion Or Motivation To Combine The References.*** As discussed previously, even assuming that the cited references in combination would suggest the claimed invention, Applicants submit that the references have not been properly combined. In order to render the claimed invention obvious, the prior art relied upon, coupled with the knowledge generally available in the art at the time of the invention, must contain some suggestion or *motivation* for the skilled artisan to modify or combine the references. *In re Fine*, 837 F.2d 1071, 1074 (1988). The mere

fact that the prior art could be so modified would not have made the modification obvious unless the prior art suggested the desirability of the modification. *In re Gordon*, 733 F.2d 900, 902.

Applicants refer to their arguments made previously, which are incorporated herein by reference. *See*, Amendment and Response submitted October 10, 2002.

In view of the foregoing, the Office has not met its burden of establishing a *prima facie* case of obviousness. First, the combination of Srinivasan, Spector and Wong does not teach or suggest the claimed invention. Furthermore, the cited references have not been properly combined. The proposed combination of references can only be achieved using hindsight reconstruction, starting from the disclosure of the Applicants and working backward. Therefore, Applicants respectfully request that the rejection of Claims 4-5, 15, 17-18, 23, 26-27, 32, 38, and 42-43 under 35 U.S.C. § 103(a) as being obvious over Srinivasan, Spector and Wong be withdrawn.

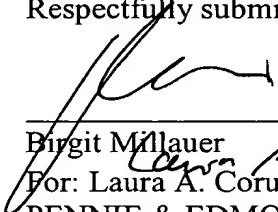
### CONCLUSION

In view of the above amendments and remarks, the subject application is believed to be in good and proper order for allowance. Early notification to this effect is earnestly solicited.

If, in the opinion of the Examiner, a telephone conference would expedite the prosecution of the subject application, the Examiner is encouraged to call the undersigned at (650) 493-4935. The commissioner is authorized to charge any underpayment or credit any overpayment to Deposit Account No. 16-1150 (order no.8484-084-999) for any matter in connection with this response, including any fee for extension of time, which may be required.

Respectfully submitted,

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Enclosures